# Randomized Controlled Study of Metformin and Sitagliptin on Long-term Normoglycemia Remission in African American Patients With Hyperglycemic Crises

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*Diabetes Care 2016;39:1948–1955 | DOI: 10.2337/dc16-0406*


## OBJECTIVE

**After intensive insulin treatment, many obese African American patients with new-onset diabetic ketoacidosis (DKA) and severe hyperglycemia are able to achieve near-normoglycemia remission. The optimal treatment to prevent hyperglycemic relapses after remission is not known.**

## RESEARCH DESIGN AND METHODS

**This prospective, 4-year, placebo-controlled study randomly assigned 48 African American subjects with DKA and severe hyperglycemia to metformin 1,000 mg daily (*n* = 17), sitagliptin 100 mg daily (*n* = 16), or placebo (*n* = 15) after normoglycemia remission. Hyperglycemic relapse was defined as fasting glucose >130 mg/dL (7.2 mmol/L) and $HbA_{1c}$ >7.0% (53 mmol/mol). Oral glucose tolerance tests were conducted at randomization and at 3 months and then every 6 months for a median of 331 days. Oral minimal model and incremental area under the curve for insulin (AUCi) were used to calculate insulin sensitivity (Si) and β-cell function, respectively. Disposition index (DI) was calculated as a product of Si and incremental AUCi.**

## RESULTS

**Relapse-free survival was higher in sitagliptin and metformin (*P* = 0.015) compared with placebo, and mean time to relapse was significantly prolonged in the metformin and sitagliptin groups compared with the placebo group (480 vs. 305 days, *P* = 0.004). The probability of relapse was significantly lower for metformin (hazard ratio 0.28 [95% CI 0.10–0.81]) and sitagliptin (0.31 [0.10–0.98]) than for placebo. Subjects who remained in remission had a higher DI (*P* = 0.02) and incremental AUCi (*P* < 0.001) than those with hyperglycemia relapse without significant changes in Si.**

## CONCLUSIONS

**This study shows that near-normoglycemia remission was similarly prolonged by treatment with sitagliptin and metformin. The prolongation of remission was due to improvement in β-cell function.**


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*Received 24 February 2016 and accepted 9 August 2016.*

*Clinical trial reg. no. NCT01099618, clinicaltrials.gov.*

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With intensive insulin treatment, more than half of obese African American patients with new-onset, unprovoked diabetic ketoacidosis (DKA) and severe hyperglycemia achieve near-normoglycemia remission from insulin (1–3). Unlike patients with type 1 diabetes, patients with DKA have a low prevalence of pancreatic autoantibodies (4–8). Near the presentation of DKA and severe hyperglycemia, these patients have defects in insulin secretion and insulin action (1,9–11). After intensive insulin treatment, many patients exhibit improved pancreatic β-cell function and insulin sensitivity (Si) and discontinue insulin therapy (near-normoglycemia remission [$HbA_{1c}$ <7%]) in favor of oral antidiabetic medications (2,10,12). Upon discontinuation of insulin, the period of near-normoglycemia may last for several months to years (10,12,13).

Despite significant improvement in insulin secretion and insulin action at the time of remission from insulin (1,14,15), many patients experience recurrence of hyperglycemia if treated with diet alone (10). Few studies have focused on the optimal treatment to prolong the period of near-normoglycemia remission in obese African American patients with DKA and severe hyperglycemia. Sulfonylureas have been shown to maintain remission for ~16 months compared with diet alone (12,16). However, sulfonylureas increase the risk of hypoglycemia (17), which may be especially detrimental in these patients during the period of near-normoglycemia remission. A small observational study by Low et al. (18) in obese pediatric and adolescent patients with DKA reported that metformin given shortly after presentation improves glycemic control and prevents readmissions for DKA; however, most patients continue to require insulin therapy during follow-up.

Sitagliptin is a dipeptidyl peptidase-4 inhibitor recommended as monotherapy for the treatment of type 2 diabetes (17). It prolongs the half-life of incretin hormones GLP-1 and gastric inhibitory polypeptide, which in turn potentiate glucose-mediated insulin release from the β-cell (19). Metformin is recommended as first-line oral therapy for the treatment of type 2 diabetes (17) and has been shown to be effective in preventing the progression to diabetes in high-risk populations (20). However, no prospective randomized controlled studies have investigated whether the use of metformin or sitagliptin is efficacious in prolongation of near-normoglycemia remission in obese African Americans with new-onset DKA and severe hyperglycemia. Therefore, we tested the hypothesis that treatment with metformin and sitagliptin monotherapy compared with placebo allows for a longer period of near-normoglycemia remission after discontinuation of insulin therapy. We also tested whether prolongation of near-normoglycemia is mediated through improvement in insulin secretion and action.

## RESEARCH DESIGN AND METHODS

### Study Subjects

This study was a single-blind randomized placebo controlled trial conducted at Grady Memorial Hospital and Emory University Hospital in Atlanta, Georgia, between September 2009 and December 2013. The study was approved by the institutional review board of Emory University. Patients were included if they were overweight or obese (BMI ≥28 kg/$m^2$), of African American ancestry, between the ages of 18 and 65 years and had new-onset, unprovoked DKA or severe hyperglycemia. Unprovoked DKA was defined as any known lack of precipitant. Patients were excluded if they had contraindications to metformin or sitagliptin; had a history of pancreatitis, moderate or severe congestive heart failure, or significant anemia; were pregnant; or were unable to consent. DKA was defined as blood glucose >250 mg/dL (13.9 mmol/L), pH <7.30, bicarbonate <18 mmol/L, and positive ketonemia defined as a β-hydroxybutyrate >3 mmol/L. Severe hyperglycemia was defined as a blood glucose >400 mg/dL (22.2 mmol/L) with pH ≥7.30 and bicarbonate ≥18 mmol/L and without ketonemia (β-hydroxybutyrate ≤3 mmol/L) (21).

### Study Protocol

Informed consent was obtained from all subjects between December 2009 and April 2013. Randomization occurred between April 2010 and July 2013, and the study was stopped in December 2013 for all subjects. Eighty-eight subjects were consented and assessed in the Grady Memorial Hospital Clinical Research Unit within 3 days of discharge after resolution of DKA and severe hyperglycemia. Anthropometric measures, family history, glucose, $HbA_{1c}$, C-peptide, and GAD antibody levels were measured at initial assessment. After discharge, all subjects were treated with intensive subcutaneous insulin to target fasting and premeal blood glucose between 70 and 130 mg/dL (3.9–7.2 mmol/L) during the next 12 weeks. To achieve target blood glucose, insulin was titrated every 2 weeks based on fingerstick glucose levels and through phone calls by the study team. Subjects were considered to be in near-normoglycemia remission if they were able to be off subcutaneous insulin for ≥1 week and have all fasting blood glucose measures <130 mg/dL (7.2 mmol/L) and/or $HbA_{1c}$ measures <7% (53 mmol/mol). In the subjects who achieved near-normoglycemia remission, $HbA_{1c}$ and fasting glucose levels were measured within 1 week after discontinuing insulin. Some subjects were able to achieve and maintain fasting blood glucose levels <130 mg/dL (7.2 mmol/L) and random blood glucose levels <180 mg/dL (10 mmol/L) after discontinuation of insulin for at least 1 week before 3 months from enrollment in the study. These subjects were considered to be in near-normoglycemia remission even if they had an $HbA_{1c}$ >7% (53 mmol/mol) and were randomized. Subjects who did not achieve fasting blood glucose levels <130 mg/dL (7.2 mmol/L) or random blood glucose levels <180 mg/dL (10 mmol/L) or $HbA_{1c}$ <7% (53 mmol/mol) or needed insulin at 12 weeks after diagnosis were considered as failing to wean from insulin and were not randomized.

At 12 weeks from enrollment, 19 subjects were unable to discontinue insulin, 18 were lost to follow-up, and 3 withdrew from the study. The 48 subjects who achieved near-normoglycemia remission were randomly assigned to sitagliptin 100 mg daily, metformin 1,000 mg daily, or placebo (one tablet daily) after 1 week of discontinuation of insulin therapy. After randomization (month 0), subjects were initially followed at the Grady Diabetes Clinic every 4 weeks until 3 months and then every 3 months until 27 months or until they experienced hyperglycemia relapse while on oral medications. Hyperglycemia relapse was defined as fasting blood glucose ≥130 mg/dL (7.2 mmol/L), a

random blood glucose measure of ≥180 mg/dL (10 mmol/L) for 2 consecutive days, or an $HbA_{1c}$ ≥7% (53 mmol/mol). All randomized subjects underwent a modified oral glucose tolerance test (OGTT) at 0, 3, 9, 15, 21, and 27 months from randomization or if they had a hyperglycemia relapse. During each study visit, subjects also received diet counseling on the plate method for meal planning (22) and encouraged to exercise at least three times a week for a minimum of 30 min/session.

### Medications

Sitagliptin and placebo were provided by Merck & Co. (Kenilworth, NJ). Metformin was obtained from the research pharmacy at Grady Memorial Hospital. All study medications dispensed to the subjects were labeled as study drug. Merck & Co. had no involvement in the study design, analyses, or writing of the article.

### Modified OGTT

After an 8- to 10-h overnight fast, all subjects were admitted to the Grady Memorial Hospital Clinical Research Unit between 8:00 and 10:00 A.M. An antecubital intravenous line was placed. After resting for 30 min, blood was drawn for fasting glucose and insulin levels. A 75-g oral glucose load was administered over 1 min. Blood draws for glucose and insulin levels were performed at 15, 30, 60, 90, and 120 min. Glucose and insulin levels were assessed at additional time points during the OGTT (15, 30, 60, 90 min) for calculations of Si and β-cell function from OGTT-derived measures.

### Measured Outcomes and Calculations

Si and β-cell function were calculated by using OGTT-derived measures. Whole-body Si was assessed by the oral minimal model. The original oral minimal model analysis was developed with a 22-point 300-min OGTT (23). A subsequent study validated the 22-point OGTT with a 7-point 120-min OGTT (24). Our modified OGTT contained six time points. The model fit using the 6-point OGTT was similar to the 120-min 7-point OGTT. Therefore, we calculated Si by using glucose and insulin levels from 6-point OGTTs on the basis of the oral minimal model. Pancreatic β-cell function was calculated from the incremental area under the curve for insulin (AUCi). For calculation of incremental AUCi, 15-, 30-, 60-, 90-, and 120-min time point insulin levels were subtracted from fasting insulin levels, and incremental AUCi was calculated with use of the trapezoidal method (25). Disposition index (DI) was calculated as the product of Si from the oral minimal model and incremental AUCi.

### Analytic Techniques

Assays for glucose, insulin, and C-peptide were performed at the Endocrinology/Lipoprotein Laboratory of the University of Tennessee Health Science Center. Glucose levels were analyzed by the hexokinase method (Beckman-Coulter, Los Angeles, CA). Insulin and C-peptide levels were measured by two-site sequential chemiluminescent immunometric assays as previously described (26). $HbA_{1c}$ and GAD antibody tests were measured at the central laboratory at Grady Memorial Hospital.

### Statistical Analyses

The primary aim of the study was to compare hyperglycemia relapse-free survival while on oral medications between the randomized groups. The secondary aims were to compare the effects of metformin and sitagliptin on β-cell function and Si compared with placebo. We also compared changes in Si and β-cell function between subjects with a hyperglycemia relapse and those who remained in near-normoglycemia remission and between subjects with initial presentation of DKA and severe hyperglycemia. For the subjects who were lost to follow-up or who withdrew from the study, values from the last documented visit were used in analyses.

This was an intention-to-treat analysis. Cox proportional hazards and log-rank tests adjusted for age were used to compare rates of hyperglycemia relapse-free survival among the metformin, sitagliptin, and placebo groups. Because of the low number of subjects with hyperglycemia relapse and censoring in the medication groups, we calculated restricted mean survival time to estimate time to hyperglycemia relapse between the combined medication and placebo groups (27,28). On the basis of the normality of the data, continuous variables were compared using ANOVA or Kruskal-Wallis test for three-group comparisons. Student *t* or Mann-Whitney *U* tests were used for two-group comparisons. Categorical data were compared using $\chi^2$ or Fisher exact test. Repeated-measures ANOVA was used to compare changes in DI, incremental AUCi, and Si over the study period. All data are expressed as mean ± SD unless stated otherwise. Statistical analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC).

Based on our previous data, we expected that 70% of obese African American patients with new-onset DKA and/or severe hyperglycemia will achieve near-normoglycemia remission (1,12). At the time of study design, there were no previously published studies in obese African Americans to determine the effect size needed to detect differences in hyperglycemia relapse-free survival. Based on our previous experience, we initially calculated that we would be able to recruit 90 subjects over a 2-year period. Accounting for a 25% attrition rate and 30% failure to wean from insulin, we calculated that we would be able to enroll 48 subjects in the study. We enrolled 88 patients from December 2009 to April 2013.

## RESULTS

Forty-eight African American subjects with DKA ($n$ = 22) and severe hyperglycemia ($n$ = 26) were included in the study. Seventeen subjects were randomly assigned to metformin 1,000 mg daily, 16 to sitagliptin 100 mg daily, and 15 to placebo. Four subjects in the metformin group, 6 in the sitagliptin group, and 1 in the placebo group were lost to follow-up. One subject in the sitagliptin group and one subject in the placebo group withdrew from the study. The overall median follow-up after insulin discontinuation was 331 days (interquartile range 102, 612 days) with no differences between randomized groups (Table 1). The subjects lost to follow-up or who withdrew from the study were in near-normoglycemia remission during their last documented study visit. There were no significant differences in baseline characteristics at presentation between subjects who withdrew and those who stayed in the study, except for $HbA_{1c}$. $HbA_{1c}$ was lower at presentation of DKA/hyperglycemia in subjects who withdrew compared with those who stayed (12.0 ± 2.3% [107 ± 25 mmol/mol] vs. 13.5 ± 2.0% [124 ± 22 mmol/mol], $P$ = 0.03) but was similar at randomization.

At presentation of DKA and severe hyperglycemia, there were no differences in

**Table 1—Clinical characteristics of obese African American subjects with DKA and severe hyperglycemia**

| | Metformin (*n* = 17) | Sitagliptin (*n* = 16) | Placebo (*n* = 15) | *P* value |
|---|---|---|---|---|
| Sex (*n*) | | | | 0.70 |
| Male | 11 | 11 | 8 | |
| Female | 6 | 5 | 7 | |
| Age (years) | 48 ± 9 | 50 ± 11 | 46 ± 13 | 0.73 |
| At diagnosis of diabetes | | | | |
| BMI (kg/m$^2$) | 35.0 ± 4.3 | 37.3 ± 10.0 | 34.9 ± 5.2 | 0.96 |
| DKA/severe hyperglycemia (*n*) | 7/10 | 10/6 | 5/10 | 0.26 |
| Family history of type 2 diabetes (%) | 71 | 88 | 80 | 0.56 |
| FBG | | | | 0.49 |
| mmol/L | 40.8 ± 13.5 | 41.7 ± 18.7 | 43.7 ± 12.2 | |
| mg/dL | 735 ± 243 | 750 ± 336 | 787 ± 219 | |
| GAD antibody positivity [*n* (%)] | 2 (12) | 0 (0)* | 3 (23)* | 0.20 |
| $HbA_{1c}$ | | | | 0.85 |
| % | 13.1 ± 2.0 | 13.1 ± 2.5 | 13.1 ± 2.3 | |
| mmol/mol | 120 ± 21 | 120 ± 27 | 120 ± 25 | |
| Fasting C-peptide (pg/L) | 2.8 ± 1.1 | 3.4 ± 1.2 | 3.1 ± 1.2 | 0.43 |
| At randomization | | | | |
| FBG | | | | 0.21 |
| mmol/L | 6.3 ± 1.0 | 6.2 ± 0.9 | 7.0 ± 1.3 | |
| mg/dL | 114 ± 18 | 111 ± 16 | 125 ± 24 | |
| $HbA_{1c}$ | | | | 0.28 |
| % | 6.2 ± 0.9 | 6.5 ± 0.7 | 6.6 ± 0.5 | |
| mmol/mol | 44 ± 10 | 48 ± 8 | 49 ± 6 | |
| Insulin dose (units/kg/day) | 0.5 ± 0.2 | 0.6 ± 0.3 | 0.8 ± 0.4 | 0.08 |
| Length of insulin use (weeks) | 9.5 ± 3.0 | 7.6 ± 3.2 | 9.2 ± 2.7 | 0.14 |
| ΔWeight from enrollment (kg) | 1.8 (−1.0, 5.9) | −0.1 (−3.5, 5.1) | −4.6 (−6.3, 0.5) | 0.08 |
| At end of study—all subjects | | | | |
| Duration of treatment† (days) | 472 (242, 716) | 194 (92, 613) | 194 (91, 579) | 0.19 |
| ΔWeight from randomization (kg) | 0 (−3.6, 3.5) | 3.3 (−0.7, 6.0) | 1.4 (−2.2, 2.9) | 0.10 |
| FBG | | | | 0.10 |
| mmol/L | 6.7 ± 1.2 | 6.9 ± 1.5 | 8.5 ± 3.2 | |
| mg/dL | 121 ± 22 | 124 ± 27 | 153 ± 58 | |
| $HbA_{1c}$ | | | | 0.04 |
| % | 6.4 ± 1.2 | 6.6 ± 1.1 | 7.6 ± 1.6 | |
| mmol/mol | 46 ± 13 | 48 ± 12 | 55 ± 22 | |
| Near-normoglycemia remission (*n*) | 12 | 12 | 4 | |
| End-of-study FBG | | | | 0.04 |
| mmol/L | 6.2 ± 1.1 | 6.1 ± 0.4 | 7.4 ± 0.8 | |
| mg/dL | 112 ± 19 | 110 ± 7 | 134 ± 15 | |
| End-of-study $HbA_{1c}$ | | | | 0.80 |
| % | 5.8 ± 0.7 | 6.1 ± 0.7 | 6.1 ± 0.5 | |
| mmol/mol | 40 ± 8 | 43 ± 8 | 43 ± 6 | |
| Hyperglycemia relapse (*n*) | 5 | 4 | 11 | |
| End-of-study FBG | | | | 0.51 |
| mmol/L | 7.9 ± 0.4 | 9.1 ± 1.3 | 8.9 ± 3.8 | |
| mg/dL | 142 ± 7 | 163 ± 23 | 160 ± 68 | |
| End-of-study $HbA_{1c}$ | | | | 0.94 |
| % | 8.0 ± 0.9 | 8.0 ± 0.9 | 8.2 ± 1.5 | |
| mmol/mol | 64 ± 10 | 64 ± 10 | 66 ± 16 | |

Data are mean ± SD or median (interquartile range) unless otherwise indicated. FBG, fasting blood glucose. *Missing GAD antibody levels for one subject in the sitagliptin group and two subjects in the placebo group. †Median time of follow-up after randomization and insulin discontinuation.

age and BMI among the metformin, sitagliptin, or placebo groups (Table 1). Although not statistically significant, both the sitagliptin and metformin groups had more men than women, whereas the placebo group had similar proportions of men and women. In the proportion of subjects with DKA or severe hyperglycemia, length and dose of insulin use before randomization (time to near-normoglycemia remission) did not differ between groups. At randomization, there were no significant changes in weight or differences in fasting glucose or $HbA_{1c}$ levels. At the end of the study, there was a significant difference in $HbA_{1c}$ ($P$ = 0.04) between the groups (Table 1). In the patients who remained in near-normoglycemia remission, there was a significant difference in fasting glucose at the end of the study (Table 1). There were no differences at diagnosis of diabetes in the subjects who remained in near-normoglycemia remission compared with those with hyperglycemia relapse at presentation (Table 2). At randomization, fasting glucose levels

**Table 2—Clinical characteristics of obese African American patients with DKA and severe hyperglycemia with near-normoglycemia remission compared with those with hyperglycemia relapse**

| | Near-normoglycemia remission ($n$ = 28) | Hyperglycemia relapse ($n$ = 20) | $P$ value |
|---|---|---|---|
| Sex ($n$) | | | 0.38 |
| Male | 19 | 11 | |
| Female | 9 | 9 | |
| Age (years) | 48 ± 10 | 49 ± 12 | 0.73 |
| At diagnosis of diabetes | | | |
| BMI (kg/m$^2$) | 35.2 ± 5.0 | 36.6 ± 9.0 | 0.96 |
| DKA/severe hyperglycemia ($n$) | 15/13 | 7/13 | 0.24 |
| Family history of type 2 diabetes (%) | 82 | 90 | 0.68 |
| FBG | | | 0.95 |
| mmol/L | 42.5 ± 16 | 41.4 ± 13.2 | |
| mg/dL | 765 ± 288 | 745 ± 239 | |
| GAD antibody positivity† [$n$ (%)] | 2 (7) | 3 (17) | 0.64 |
| $HbA_{1c}$ | | | 0.75 |
| % | 13.2 ± 2.2 | 13.0 ± 2.2 | |
| mmol/mol | 121 ± 24 | 119 ± 24 | |
| Fasting C-peptide (pg/L) | 3.3 ± 1.1 | 2.8 ± 1.3 | 0.25 |
| At randomization | | | |
| FBG | | | 0.007 |
| mmol/L | 6.1 ± 0.9 | 7.0 ± 1.1 | |
| mg/dL | 110 ± 17 | 126 ± 20 | |
| $HbA_{1c}$ | | | 0.14 |
| % | 6.3 ± 0.8 | 6.7 ± 0.5 | |
| mmol/mol | 49 ± 12 | 60 ± 16 | |
| Insulin dose (units/kg/day) | 0.6 ± 0.2 | 0.7 ± 0.4 | 0.67 |
| Length of insulin use (weeks) | 8.6 ± 3.1 | 9.1 ± 2.9 | 0.57 |
| ΔWeight from enrollment (kg) | −0.4 (−6.9, 1.8) | 0.8 (−5.4, 4.5) | 0.24 |
| At end of study | | | |
| ΔWeight from randomization (kg) | −0.4 (−2.5, 3.1) | 2.1 (−0.4, 5.6) | 0.11 |
| FBG | | | <0.0001 |
| mmol/L | 6.3 ± 0.9 | 8.7 ± 2.8 | |
| mg/dL | 114 ± 17 | 156 ± 50 | |
| $HbA_{1c}$ | | | <0.0001 |
| % | 6.0 ± 0.7 | 8.1 ± 1.2 | |
| mmol/mol | 42 ± 8 | 65 ± 13 | |

Data are mean ± SD or median (interquartile range) unless otherwise indicated. FBG, fasting blood glucose. †Missing GAD antibody levels for one subject in the near-normoglycemia remission group and two subjects in the hyperglycemia relapse group.

were higher in subjects who experienced hyperglycemia relapse than in those who remained in remission (Table 2). At the end of the study, fasting glucose and $HbA_{1c}$ levels were higher in the subjects who experienced hyperglycemia relapse (Table 2).

Hyperglycemia relapse-free survival was significantly higher in the metformin and sitagliptin groups than in the placebo group ($P$ = 0.015) (Fig. 1). The 2-year failure rate was higher in the placebo than in the sitagliptin (77% vs. 44%, $P$ = 0.113) or metformin (77% vs. 34%, $P$ = 0.013) groups. Compared with placebo, patients randomized to metformin (hazard ratio 0.28 [95% CI 0.10–0.814]) and sitagliptin (0.31 [0.10–0.98]) were ~70% less likely to have a hyperglycemia relapse. However, there was no difference in hyperglycemia relapse-free survival between metformin and sitagliptin ($P$ = 0.75) (Fig. 1). The restricted mean time to hyperglycemia relapse in the combined metformin and sitagliptin groups was significantly higher than placebo (480 vs. 305 days, $P$ = 0.004).

We also assessed whether being on medication decreased the severity of hyperglycemia relapse. Because only a small number of subjects experienced relapse in the medication groups (metformin [$n$ = 5], sitagliptin [$n$ = 4]) compared with placebo ($n$ = 11), we combined the metformin and sitagliptin groups. There were no significant differences in $HbA_{1c}$ (8.0 ± 0.8% [64 ± 9 mmol/mol] vs. 8.2 ± 1.5% [66 ± 16 mmol/mol], $P$ = 0.79) or blood glucose (152 ± 18 mg/dL [8.4 ± 1 mmol/L] vs. 160 ± 68 mg/dL [8.9 ± 3.8 mmol/L], $P$ = 0.65) levels at the time of hyperglycemia relapse between the placebo group and the combined metformin and sitagliptin group. In the placebo group, 3 of the 11 subjects who experienced hyperglycemia relapse presented to the emergency department with a glucose level >400 mg/dL (22.2 mmol/mol) or DKA. None of the patients in the metformin and sitagliptin group had a hyperglycemia relapse necessitating a visit to the emergency department or admission to the hospital.

The difference in hyperglycemia relapse was explained by improvements in β-cell function. Over the course of the study, DI ($P$ = 0.02) and incremental AUCi ($P$ < 0.001) were significantly higher in subjects who remained in near-normoglycemia remission compared with those who had a hyperglycemia relapse without any differences in Si ($P$ = 0.75). There was a significant interaction between remission status and study visit for both Si ($P$ = 0.01) and DI ($P$ = 0.02), suggesting a different pattern of change in Si and DI over time between subjects with near-normoglycemia remission and hyperglycemia relapse. The difference in DI and incremental AUCi was not present at randomization in the subjects who stayed in near-normoglycemia remission compared with those who experienced a hyperglycemia relapse (Fig. 2*A* and *B*). At the last documented follow-up, there were no differences in Si (Fig. 2*C*); however, DI ($P$ = 0.02) and incremental AUCi ($P$ < 0.001) were significantly higher in subjects who stayed in near-normoglycemia remission than in those who had a hyperglycemia relapse at the end of the study (Fig. 2*A* and *B*). Comparison across treatment groups showed no differences at randomization, over the course of the study, or at the last follow-up for DI, incremental AUCi, or Si (data not shown). Similarly, a comparison of subjects with an initial presentation of DKA and severe hyperglycemia showed no differences in Si, incremental AUCi, or DI at randomization, over the course of the study, or at the last follow-up (data not shown). Although there were no significant changes in weight, we performed analyses adjusting for changes in weight throughout the course of the study. No differences

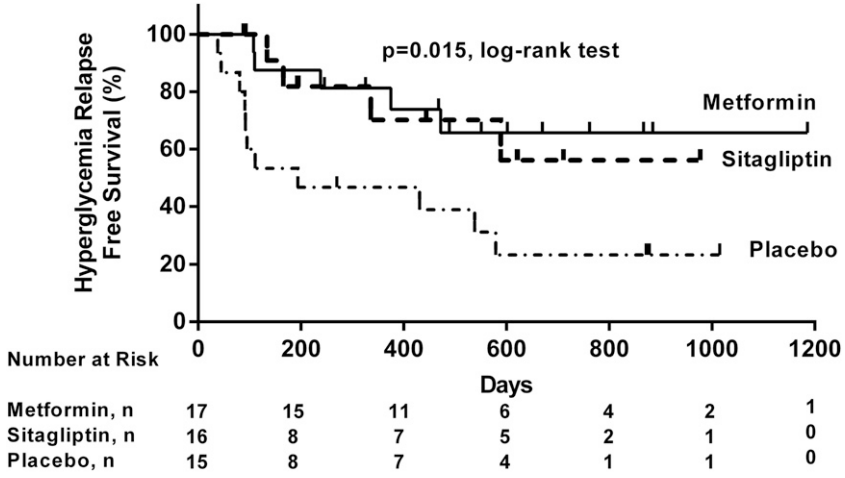


**Figure 1**—Cox proportional hazards of failure-free survival among metformin, sitagliptin, and placebo in obese African American patients presenting with DKA and severe hyperglycemia. A significant difference was found among the placebo, metformin, and sitagliptin groups ($P$ = 0.015), but no significant difference was found between the sitagliptin and metformin groups ($P$ = 0.75).

were found in Si, incremental AUCi, or DI compared with unadjusted analyses.

## CONCLUSIONS

To our knowledge, this is the first randomized controlled longitudinal study to determine the efficacy of metformin and sitagliptin in avoiding recurrence of hyperglycemia in African American subjects with DKA and severe hyperglycemia. The study shows that both metformin and sitagliptin significantly prolong near-normoglycemia remission in subjects with both DKA and severe hyperglycemia and that these subjects are ~70% less likely to experience hyperglycemia relapse than those taking placebo. The prolongation of near-normoglycemia remission was due to improvement in insulin secretion in subjects who remained in remission compared with those who experienced hyperglycemia relapse as shown by the incremental AUCi.

Previous studies by our group (1) and others (6,10,13) have shown that subjects with DKA and severe hyperglycemia experience significant improvement in β-cell function after 8–12 weeks of intensive treatment, which allowed for discontinuation of insulin in ~70% (1). The period of near-normoglycemia remission is variable, with some studies reporting remission lasting between 6 and 120 months (10,13). Despite the initial improvement, most obese African American patients with DKA and severe hyperglycemia (12,16) have a gradual decline in their β-cell function (10) with continued insulin resistance (15) if treated with diet alone. Previous studies with sulfonylureas showed prolongation of near-normoglycemia remission in obese African American patients with an initial presentation of DKA and severe hyperglycemia (12,16), but sulfonylurea treatment may increase the risk for hypoglycemia and weight gain. In the current study, we significantly prolonged near-normoglycemia with metformin and sitagliptin in subjects with an initial presentation of both DKA and severe hyperglycemia without significant changes in weight. In addition, in the subjects who experienced hyperglycemia relapse, those taking metformin and sitagliptin had a milder presentation of relapse than those taking placebo.

Prevention of hyperglycemia relapse was through improvement in β-cell function. In this study, subjects who remained in near-normoglycemia remission had a significant improvement in insulin secretion compared with those who experienced hyperglycemia relapse. There were no significant changes in Si between subjects in remission and those with hyperglycemia relapse. This finding is consistent with previous studies in obese African Americans with DKA and severe hyperglycemia (2,10) and in patients with type 2 diabetes from the UK Prospective Diabetes Study, which showed that deteriorating β-cell function rather than insulin resistance is the primary reason for deterioration of glucose control (29). The current findings are also similar to those of reports in subjects with newly diagnosed type 2 diabetes in whom intensive therapy and tight glucose control resulted in significant improvement in β-cell function (30,31).

There are several limitations to this study. Subjects lost to follow-up or who withdrew from the study had a lower $HbA_{1c}$ at presentation with DKA and severe hyperglycemia and were in remission at the last documented study follow-up. Most of these subjects were also in the sitagliptin and metformin groups. Therefore, withdrawal of these subjects could have underestimated changes in insulin secretion and Si in the metformin and sitagliptin groups. At the time of study design, no data were available on the effect sizes needed to detect differences in long-term hyperglycemia-free survival. We designated the number needed based on feasibility of recruitment over the study period. Therefore, the study was likely underpowered to detect mechanistic differences contributing to near-normoglycemia remission between treatment groups as well as between subjects with DKA and severe hyperglycemia. Another limitation was that subject follow-up was variable and that the study was stopped in December 2013 irrespective of when subjects were recruited. Therefore, subjects recruited later were followed for a shorter period than those recruited earlier. If all subjects had equivalent follow-up periods, it may have been possible to discern significant differences in Si or insulin secretion between randomized groups. Of note, insulin doses at randomization in the metformin and sitagliptin groups trended lower than those in the placebo group. In addition, fasting glucose levels at randomization were lower in subjects who stayed in near-normoglycemia remission than in those who experienced hyperglycemia relapse. However, there were no differences in Si, incremental AUCi, or DI between the groups at randomization, suggesting that the lower insulin needs in the metformin group and fasting blood glucose levels in the subjects who stayed in near-normoglycemia remission were likely not the reason for the sustained near-normoglycemia remission.

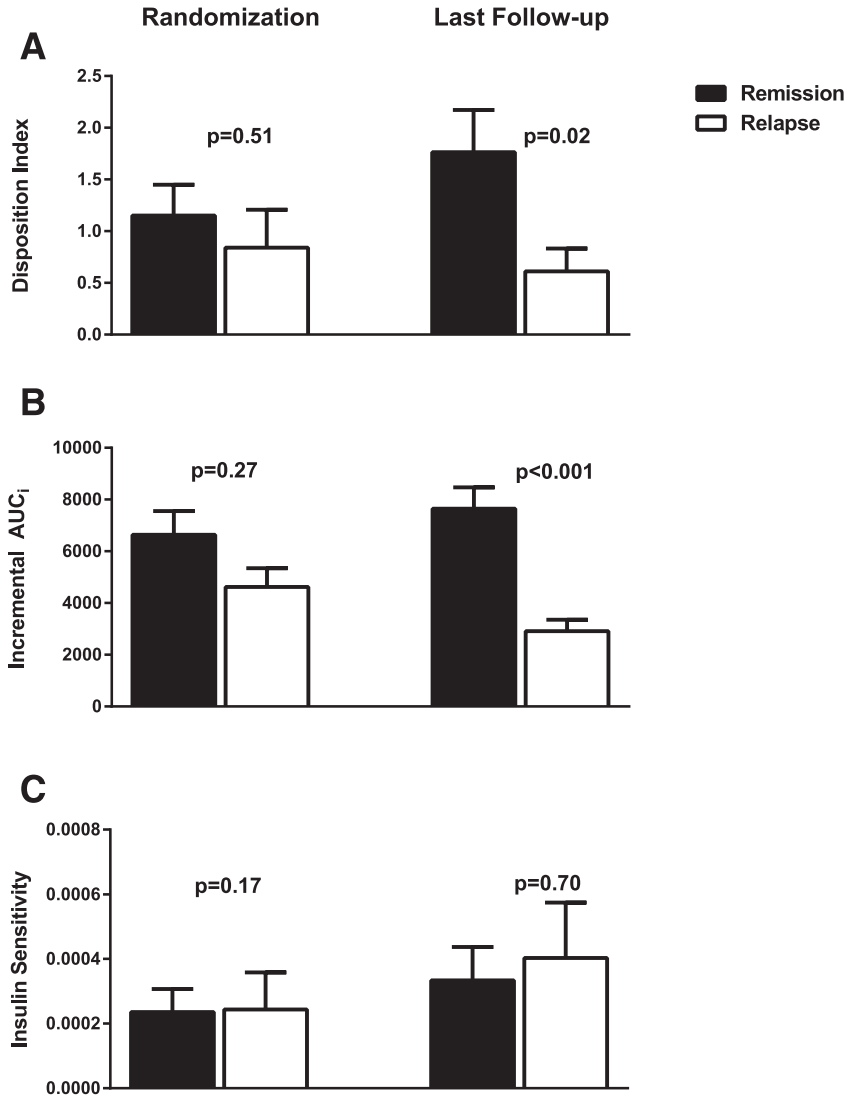


**Figure 2**—DI, incremental AUCi, and Si at randomization and last follow-up. At randomization OGTT, no significant differences were found in DI, incremental AUCi, or Si in subjects who remained in near-normoglycemia remission at the end of the study compared with those with hyperglycemia relapse. During the last follow-up OGTT, subjects who remained in remission had higher DI and incremental AUCi than those who had a relapse (*A* and *B*) without a difference in Si (*C*).

In summary, this study showed that near-normoglycemia remission is prolonged by monotherapy with either metformin or sitagliptin in obese African American patients with DKA and severe hyperglycemia. The study also showed that near-normoglycemia can be explained by changes in β-cell function. We did not find any differences in Si or β-cell function between subjects with an initial presentation of DKA and severe hyperglycemia. Because there were no differences in prolongation of near-normoglycemia remission between metformin and sitagliptin, either medication can be used to prolong and maintain near-normoglycemia remission in obese African American patients with DKA and severe hyperglycemia.

**Funding.** This work was supported in part by National Institute of Diabetes and Digestive and Kidney Diseases grant K08-DK-0830361 (D.D.S.), National Institutes of Health Clinical Center grant M01-RR-00039 (Atlanta Clinical & Translational Science Institute) (G.E.U.), and the Jacobs Family Foundation Research Fund (G.E.U.). G.E.U. is also supported in part by a research grant from the American Diabetes Association (1-14-LLY-36) and Public Health Service grant UL1-RR-025008.

**Duality of Interest.** P.V. and F.J.P. have received consulting fees from Merck & Co. D.S. has received fees and/or honoraria for participation in advisory committees from Janssen, Sanofi, and Boehringer Ingelheim. G.E.U. has received unrestricted research support for inpatient studies (to Emory University) from Merck & Co., Novo Nordisk, Boehringer Ingelheim, and AstraZeneca and has received consulting fees for participation in advisory boards from Sanofi and Merck & Co. No other potential conflicts of interest relevant to this article were reported.

**Author Contributions.** P.V. contributed to the data analyses and writing and editing of the manuscript. D.D.S. contributed to the study design and conduct, data analysis, and editing of the manuscript. D.S. and L.P. contributed to the data analysis and editing of the manuscript. I.A., W.D., M.H., and F.J.P. contributed to the conduct of the study and editing of the manuscript. G.E.U. contributed to the study design and conduct and editing of the manuscript. P.V. and D.D.S. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Prior Presentation.** Parts of this study were presented orally at the 74th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 13–17 June 2014.

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